repulsion grounds. Either of these would lead to trans product.[13,14]

Treatment of 8 with sodium hydride–benzene (1 equiv of 8 and 1.6 equiv of base) at room temperature for 96 hr gave a 74% yield of dihydrofuran derivative **14** [$\lambda_{max}^{CHCl_3}$ 1755, 1730, 1690, 1644 cm^{-1}; λ_{max}^{MeOH} 255 nm (ϵ 12,200); *m/e* 286 (P); nmr (Chart I[12]). While we do not rule out the possibility of small amounts of products derived from C-alkylation, O-alkylation is again the predominant pathway. It should be noted that in the case of closely related compound **15**, which differs from 8 only by carboalkoxyl *vs.* acetyl deprotonation induces rapid scrambling of the esters,[1c] undoubtedly *via* homoconjugate attack. Whether such an equilibrium is concurrent with the O-alkylation reaction is not known.

In an attempt to study the consequences of generating a monostabilized enolate in an intramolecular relationship to a cyclopropane ring, compound **10** was treated with sodium hydride–benzene and a trace of methanol. There was thus obtained, in 65% crude yield, the difficultly crystalline Dieckmann product **16**,[5,15] mp 35°. The predominant tautomeric form is tentatively assigned as shown, on the basis of the chemical shifts (Chart I[12]) which seem most compatible with the presence of an allylic type methyl. After Dieckmann cyclization had been undergone, possibility of ring mutation is blunted since an endocyclic type of S$_N$2 displacement would now be required.[16]

Acknowledgments. This research was supported by PHS Grant No. 11207-10. Nmr spectra were measured on the Mellon–Pitt–Carnegie (MPC) 250-MHz facility supported by NIH Grant RR-00292-07.

Supplementary Material Available. The experimental procedures for the reactions described in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2658.

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(6) This experiment was conducted by Dr. M. Yamamoto.

(7) A formal interpretation of this process would involve insertion of the copper carbenoid into the enolic double bond followed by ring opening of the resultant cyclopropanol.

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(12) The nmr spectra were measured at 250 MHz. Chemical shifts are reported in δ units from tetramethylsilane as an internal standard. When necessary, decoupling was employed for shift assignments. The spectra of **11** and **12** were measured in deuteriochloroform. Those of **13**, **14**, and **16** were measured in carbon tetrachloride.

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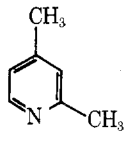
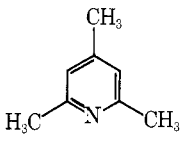
Selective Metalations of Methylated Heterocycles. III. Thermodynamic *vs.* Kinetic Control

Summary: Ethereal solutions of 2-lithiomethyl-4-methylquinoline (**4a**) can be isomerized to 4-lithiomethyl-2-methylquinoline (**4b**) and vice versa as a function of solvent and time.

Sir: Recently, selective metalations of one or the other of two methyl groups substituted 2 or 4 to the ring nitrogen atoms of 2,4-lutidine (**1**), 2,4,6-collidine (**2**), and 2,4-dimethylquinoline (**3**) as a function of the metalating agent were described.[1] In essence, exclusive metalations of the 2- or 4-methyl groups of such compounds were realized with *n*-butyllithium in ether–hexane and sodium amide in liquid ammonia, respectively.



1



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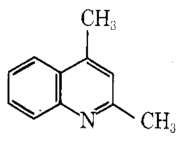
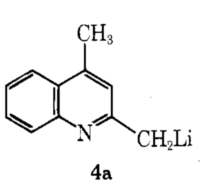
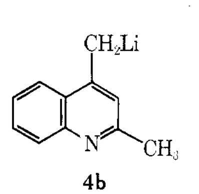


3

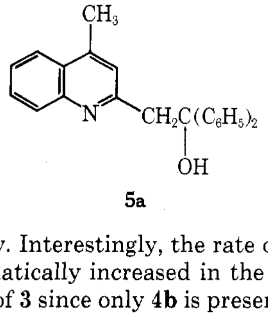
We now wish to report that, though selective metalations of polymethylated pyridines and quinolines continue to be realized, different organolithium derivatives can be cleanly obtained as a function of the ethereal solvent and the reaction periods employed. Thus, metalation of **3** by *n*-butyllithium in THF–hexane gives only **4a** after 1 hr, mixtures of **4a** and **4b** after 24 hr, and only **4b** after 144 hr. That **4a** and/or **4b** were indeed present was demonstrated by condensation with benzophenone to afford **5a**[1] or **5b**,[1] respectively. Interestingly, the rate of isomerization of **4a** to **4b** is dramatically increased in the presence of an extra equivalent of **3** since only **4b** is present at the end of 1 hr.



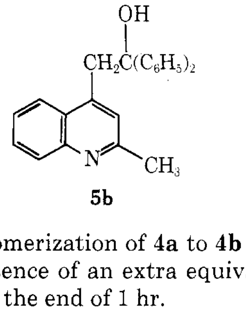
4a



4b



5a

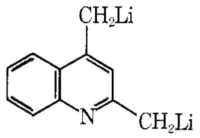


5b

In contrast to the conversion of **4a** to **4b** in THF–hexane, **4a**, prepared from **3** and *n*-butyllithium in ethyl ether–hexane, did *not* isomerize to **4b** even after 96 hr. In fact, the opposite could be realized. Thus, **4b** was prepared from dimethylaminolithium and **3** in THF–hexane and the reaction mixture was divided into two parts. One part was trapped with benzophenone to afford **5b**. The other part was evaporated to dryness and treated with ethyl ether, **3**, and benzophenone to give only **5a**.

It can be concluded from the above that the formation of solvated organometallics **4a** and **4b** is either kinetically or thermodynamically controlled depending on the solvent. Thus, **4a** solvated by THF is the kinetic product while **4a** solvated by ethyl ether is the thermodynamic product. On the other hand, **4b** solvated by THF is the thermodynamic product while **4b** solvated by ethyl ether is the kinetic product. The relative thermodynamic stabilities of solvated **4a** and **4b** can be rationalized on the basis that the less sterically bulky THF interacts less with the peri-hydrogen atom of **4b** than does ethyl ether.

These isomerizations are similar to those obtained with excess alkylbenzenes and alkylsodium and potassium reagents,[2] and to those realized with certain alkali derivatives of benzyldimethylamine,[3] though no solvent effects were reported. The interconversions of **4a** and **4b** probably occur *via* a small amount of unionized **3** but may also involve dianion **4c**; compounds like **4c** have recently been prepared from polymethylpyridines.[4]



4c

In conclusion, synthetically useful side-chain metalations of six-membered polyalkyl nitrogenous aromatic heterocycles can be realized provided that careful attention is directed toward the choice of solvent, metalating agent, metallic cation, and time. Studies on systems other than **3** are currently under investigation in these laboratories.

Supplementary Material Available. Experimental data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2659.

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A Unique Example of Virtual Proton–Proton Coupling in Purine Nucleosides

Summary: A unique long-range virtual coupling between C-1′ H and C-3′ H of 2′-*O*-benzyl derivatives of adenosine and inosine is reported.

Sir: Our interest in developing techniques for the chemical synthesis of oligoribonucleotides of defined chemical structure has led to the synthesis of a number of ribonucleosides having the 2′- or 3′-hydroxyl function selectively protected by a benzyl[1] or *p*-methoxybenzyl[2] group. It was of interest to study the conformation in solution of certain of these benzyl ribonucleosides, since molecular models suggested that overlap (stacking) of the benzene and heterocyclic moieties could occur in the 2′-*O*-benzyl series but not in the 3′-*O*-benzyl nucleosides (Figure 1). As has been previously shown by a number of groups,[3–5] pmr spectroscopy in aqueous (D_2O) solution affords an excellent method of evaluating a stacking interaction between two or more "heteroaromatic" bases in a molecule.

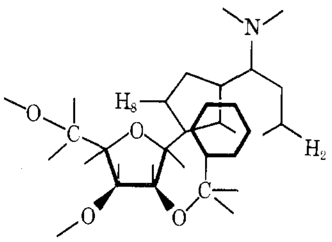

Figure 1

Examination of the pmr spectra of 2′-*O*-benzyladenosine (**1**) and 2′-*O*-benzylinosine (**2**) in D_2O solution (~0.10 *M*) at 60 MHz revealed a striking anomaly in the signal attributable to C-1′ H. β-D-Ribofuranosylpurine spectra normally exhibit $J_{1',2'}$ values of around 6 Hz and the C-1′ H signal appears as a clean doublet. This was indeed the case for **1** and **2** in $(CD_3)_2SO$ solutions. In D_2O, however, the signal due to C-1′ H appeared as a complex multiplet. The spectrum of 2′-*O*-benzyluridine, on the other hand, revealed an entirely normal doublet $J_{1',2'} = 6.0$ Hz) attributable to the C-1′ H signal.

As previously observed,[1,2] 2′-*O*-benzyl ribonucleosides in aqueous solution appear to exist in a "folded" conformation (Figure 1) in which the benzene ring is stacked with the heterocyclic moiety. It was, therefore, of interest to determine if an elevated temperature would lead to unstacking and whether this would have an effect on the multiplicity of the C-1′ H signal. Therefore, pmr spectra were recorded of a 0.046 *M* solution of **1** in D_2O at 30° and at 70°. Unstacking at the higher temperatures was confirmed by the downfield shifts of 0.06, 0.13, 0.10, and 0.10 ppm for C-8 H, C-2 H, the phenyl protons, and C-1′ H, respectively. The differential shifts of C-8 H and C-2 H support a conformational model in which the benzene ring is stacked primarily over the pyrimidine ring of the purine. In addition to the deshielding experienced by C-1′ H over this temperature range, the signal collapsed from the multiplet to a clean doublet ($J_{1',2'} = 5.5$ hz). This observation strongly suggested that the observed multiplicity arose from a conformationally dependent long-range coupling between C-1′ H and another proton in the molecule resulting from stabilization of a specific ribose conformation by an intramolecular stacking interaction. Unstacking at higher temperature presumably permits the establishment of a mobile equilibrium of conformers. Because of the complexity of the spectrum arising from the sugar portion of the molecule